The role of Trastuzumab Emtansine as a novel-targeted therapy for HER2+ breast cancer: A systematic review

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ABSTRACT
Trastuzumab is the first humanized monoclonal antibody targeted against the human epidermal growth factor receptor 2 (HER2), tyrosine kinase receptor, that has displayed excellent clinical activity in HER2-overexpressing breast cancer. Despite this, the majority of patients with metastatic HER2-positive breast cancer who initially demonstrate good clinical responses to trastuzumab within the first year of initiation of treatment start to develop resistance within 1 year of initiation of treatment. Even patients on trastuzumab-based chemotherapy regimens have been shown to progress within 1 year of therapy. The antibody-drug conjugate trastuzumab-DM1 (T-DM1) was designed to combine the biological activity of trastuzumab with the targeted delivery of a highly potent antimicrotubule agent, DM1 (N-methyl-N-[3-mercaptop-1-oxopropyl]-l-alanine ester of maytansinol), a maytansine derivative, to HER2-positive breast cancer cells. Phase I and II clinical trials of T-DM1 as a single agent and in combination with paclitaxel, docetaxel, and pertuzumab have shown clinical activity and a favorable safety profile in HER2-positive metastatic breast cancer patients. The EMILIA study, a randomized phase III trial, has shown that T-DM1 provided objective tumor responses and significantly improved progression free survival and overall survival compared to lapatinib and capecitabine combination in HER2-positive metastatic breast cancer patients treated with a prior taxane and trastuzumab regimen. Based on these results, T-DM1 has been indicated in the management of patients with advanced and early stage HER2-positive breast cancer. In this review, we summarize evidence from clinical studies and aim to discuss the potential clinical and therapeutic implications of T-DM1 therapy in the management of HER2-positive breast cancer.

Key words: Breast cancer, HER2, T-DM1, trastuzumab-emtansine

INTRODUCTION
Breast cancer is the most common malignancy in women and it is the second leading cause of cancer related mortality in women. As per 2011 statistics, it affected 230,480 women and was responsible for 39,520 deaths.[1]

It is well known that human epidermal growth factor receptor 2 (HER2) receptors are overexpressed in 20% of breast cancers and is a poor prognostic marker.[2,4] HER2, also known as neu, ErbB2, CD340, or p185 protein, is a 185 kDa transmembrane receptor protein. It is a member of the epidermal growth factor receptor (EGFR) family and is encoded by the proto-oncogene HER2/neu. When overexpressed, it can be as dense as 1.5 million copies per tumor cell, making it ideal for targeted therapy.[5] Trastuzumab (Herceptin) is the first humanized monoclonal antibody that binds to the extracellular domain IV of the HER2 receptor and targets the HER-2 pathway.


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Cytotoxic drugs clearly cause some degree of systemic toxicity and hence a limited therapeutic index. This gave birth to the novel idea of antibody drug conjugate (ADC). The concept is to combine the target specificity of the monoclonal antibody and the potent action of the cytotoxic agent. The only Food and Drug Administration of the United States of America (USFDA)-approved ADC’s currently are Gemtuzumab ozogamicin (indicated for use in CD33+ acute myeloid leukemia) and Brentuximab vedotin (resistant or relapsed Hodgkin’s Lymphoma).[8,9] More recently, the USFDA approved Trastuzumab emtansine or T-DM1, an ADC for the management of HER-2 + metastatic breast cancer (MBC). The objective of this review is to discuss the clinical studies and pharmacological properties of T-DM1 and its benefits in patients with resistant or relapsed HER-2 positive breast cancer.

CHEMISTRY

Antigen drug conjugates (ADCs) are molecules containing cytotoxic agents linked to antigen-specific monoclonal antibodies via chemical linkers.[10-12] ADC therapy increases the therapeutic index of the drug and reduces systemic side effects due to highly specific targeting mechanisms.[12,13] The important parameters for developing this novel therapeutic ADC include target antigen selection, conjugate internalization by tumor cells, drug potency, and stability of the linker between drug and antibody. The linker should be able to stabilize the ADC in circulation and once the compound enters the cell it should release the cytotoxic agent in a manner that does not alter its effect.

Trastuzumab emtansine is the third USFDA-approved ADC. It is also the first ADC that is directed specifically against HER2 positive tumor cells.

Trastuzumab is a humanized monoclonal antibody directed against HER2 positive tumor cells. Emtansine/DM1 (N-methyl-N-[3-mercaptop-1-oxopropyl]-l-alanine ester of maytansinol) is a maytansinoid derivative. It is a highly potent antimicrotubule drug with a cytotoxicity 200-fold greater than vincristine but it has a lower therapeutic index.[10-13] It has been shown that trastuzumab possesses synergistic activity when combined with antitubulin agents. Hence, DM1 was thought to be an ideal cytotoxic agent to link with it. Each Trastuzumab-DM1 (TDM1) molecule has 3.5 molecules of DM1 attached to one antibody.[14] It consists of Trastuzumab connected to DM1/ emtansine through a stable nonreducible thioether linkage (N-succinimidyl-4-cyclohexane-1-carboxylate) (SMCC) group.[15] It is directed at the domain IV of HER2 ECD. HER2 represents a logical target for ADC therapy because it is highly differentially expressed on HER2 positive breast tumor cells, that is, 1.5-2 million copies per cell. This targeted drug delivery system ensures enhanced clinical efficacy with reduced systemic nonspecific clinical toxicity. This is because, DM1 remains inactivated and therefore does not have clinical nonspecific toxicities in the conjugated form. Also, the intracellular metabolite of TDM1 is a zwitterion that does not cross the plasma membrane of neighboring cells and so contributes to its safety profile.[15-17]

PHARMACODYNAMICS

TDM1 binds to the HER2 positive tumor cell that results in the internalization of the complex via endocytosis. This is followed by intralysosomal proteolytic degradation and the resultant formation of metabolites, Lys-MCC-DM1.[18-20] These molecules after being released into the cytoplasm attach to microtubules and destabilize them. This prevents mitosis and eventually leads to cell death. The conjugation does not affect the affinity of trastuzumab to the HER2 receptors. The preclinical activity of TDM1 has been tested in trastuzumab and/or lapatinib refractory models.[19-21] Studies using reverse transcriptase polymerase chain reaction showed that a level of HER2 mRNA expression above the median had a higher overall response rate (ORR). Thus, TDM1 is not only specific for HER2 positive MBC but the response is directly proportional to the density of HER2 receptors located on the tumor cell.[21-23]

PHARMACOKINETICS

The pharmacokinetic profile (PK) was studied in trastuzumab resistant mouse models. Here, TDM1 did not react with neu, the rodent ortholog of HER2, which resulted in no difference in PK between tumor bearing and nonbearing mice. On the contrary, Trastuzumab-binding species showed a dose-dependent decrease in clearance associated with increasing dose.[22,24-27]

Mean clearance was 21.2 to 27 ml/d/kg at doses 0.3 to 1.2 mg/kg. This clearance decreased to 6.9 from 12.9 ml/d/kg for dosages above 1.2 mg/kg indicating a longer half-life. At MTD (maximal tolerated dose) of 3.6 mg/kg every 3 weeks, the clearance of the drug is 12.9 ml/d/kg and terminal half-life is 3.5-3.96 days.

An average maximum concentration (Cmax) was 5.36 ng/ml in cycle 1 and 5.97 ng/ml in cycle 4. This implies that clearance of TDM1 is more rapid than trastuzumab. Population PK model was presented by Gupta et al.[27] It was updated by Lu et al. where data were collected from 671 patients using 9 934 of TDM1 conjugate serum concentration time points to determine the effects of covariates on PK of TDM1 and to identify clinical factors affecting TDM1 exposure in patients.[28] The study showed terminal half-life of 3.93 with clearance of 0.68 l/day and a central volume of 3.13 l.
The interindividual variability in TDM1 clearance after adjusting for covariates was <20%. The level of albumin, liver enzymes, tumor burden, body weight were statistically significant covariates, but their effect on TDM1 exposure was clinically insignificant. About 4.3% patients developed antibodies to TDM1 repeated doses, but no change in PK, safety profiles or efficacy was observed in these patients.

Pharmacokinetics of TDM1 was also studied in Sprague Dawley rats.[29] It was found that following administration of radiolabeled TDM1, circulating TDM1 level was higher as compared to DM1 level, indicating the strength of the conjugate. Inside the cell, TDM1 is metabolized by CYP3A4 and CYP3A5. It is shown in various phase I and II clinical studies that TDM1 is neither an inducer nor inhibitor of CYP isofom. There was no accumulation or tissue retention by day 14 and 80% of the drug was excreted in feces and a small fraction in urine.

**CLINICAL TRIALS**

Phase I study TDM3569g, the first multicenter, open label, dose-escalation, clinical study to effectively evaluate the safety, pharmacokinetics and tolerability in 24 patients with advanced HER2-positive breast cancer who had previously used a trastuzumab-based regimen. T-DM1 was administered at various doses on a weekly or every 3-weekly schedule by intravenous infusion over 30 to 90 min.

For the 3-weekly schedule, T-DM1 was administered to the 24 patients at 0.3 to 4.8 mg/kg.[30] Dose-limiting toxicity (DLT) was observed at the 4.8 mg/kg dose with grade 4 thrombocytopenia in two of three patients. The maximum tolerated dose (MTD) was, thus, defined as 3.6 mg/kg every 3 weeks. The most common adverse events (AEs) were thrombocytopenia (54.2%), elevated transaminases (41.7%), fatigue (29.2%), and nausea (25%). Most AEs were mild and grade 1 or grade 2. In the patients who received T-DM1 at doses greater than 1.2 mg/kg there was evidence of some thrombocytopenia observed. The confirmed response rate (RR) in nine patients treated at MTD and with measurable disease was 44%. In a group of 15 patients receiving 3.6 mg/kg every 3 weeks, the clinical benefit rate (CBR; RR plus stable disease at 6 months) was 73%.

A group of 28 patients in total received T-DM1 at 5 dose levels (1.2 mg/kg, 3 patients; 1.6 mg/kg, 3 patients; 2.0 mg/kg, 3 patients; 2.4 mg/kg, 16 patients; 2.9 mg/kg, 3 patients) on a weekly schedule.[30] In two of three patients at 2.9 mg/kg a DLT occurred on day 8 of the first cycle: A grade 3 thrombocytopenia and a grade 3 elevated AST. The MTD was 2.4 mg/kg resulting in a cumulative dose of 7.2 mg/kg in a 21-day cycle. The starting dose of this phase I study was based on one-third of the MTD for the 3-weekly schedule of 3.6 mg/kg q3w. In total, 9 of 28 patients experienced a grade 3/4 AE related to study drug and most frequent AEs were increased AST/alanine transaminase (ALT) and thrombocytopenia. PK was dose proportional at a dose >1.2 mg/kg with mild accumulation for T-DM1 and trastuzumab. Objective partial responses were reported in 13 (46.4%) patients with median response duration of 18.6 months. The CBR was 57% (16 of 28 patients). Based on these clinical results and dosing convenience, it was decided that T-DM1 at 3.6 mg/kg every 3 weeks would be utilized for further clinical development.

The aim of the phase II study TDM4258g was to further study the clinical safety profile and efficacy of T-DM1 administered at a dose determined by the previous phase I study, 3.6 mg/kg every 3 weeks.[23] In this single-arm trial, 112 HER2-positive MBC patients were selected who had tumor progression after prior treatment with HER2-directed therapy and had received prior chemotherapy. The objective response rate (ORR) by independent assessment was shown to be 25.9%. The median duration of response was not reached due to insufficient events. The median PFS was 4.6 months. The response rates were found to be higher in patients whose tumors expressed more than median HER2 levels by quantitative reverse transcriptase polymerase chain reaction for HER2 expression, compared with patients who had less than median HER2 levels. T-DM1 has been shown to be well tolerated and most adverse effects seen were similar to those in phase I studies. Most adverse events were grade 1 or 2 and the most frequently seen adverse events were fatigue (60.7%), nausea (50%), and headache (40.2%). The most common grade 3 adverse events were hypokalemia (8.9%), thrombocytopenia (8%) and fatigue (4.5%). No cardiotoxicity was reported with T-DM1.

In the second open-label, single arm, multicenter phase II study TDM4374 g, 3.6 mg/kg T-DM1 was given intravenously every 3 weeks to 110 patients with HER2-positive MBC who had previously treated with anthracycline, taxane, capecitabine, trastuzumab, and lapatinib.[31] The median number of prior agents used in the metastatic setting was seven and 99% of patients had been treated with at least five agents prior to this study. The aim of this study was to determine the efficacy of T-DM1 in HER2-positive MBC patients who have previously received all standard HER2-directed therapies. The ORR was found to be 34.5%, CBR 48.2%, median PFS 6.9 months and median duration of response 7.2 months. Most AEs were grade 1 or 2, the most common ones being fatigue (62%), nausea (37%), and thrombocytopenia (33%). The most frequent grade 3 and 4 side effects were thrombocytopenia (9.1%), fatigue (4.5%), and cellulitis (3.6%). No patients experienced 25% or more decrease of left ventricular ejection fraction (LVEF) at the conclusion of the study.
Another phase II study in the first-line setting, TDM4450, was a randomized, open-label, two-arm, multicenter study aimed at investigating the efficacy and safety of T-DM1 and trastuzumab plus docetaxel in patients with recurrent, advanced, or metastatic breast cancer. In the T-DM1 arm ORR was 64%, whereas it was 58% in trastuzumab arm. The PFS was significantly improved with T-DM1 compared to trastuzumab (14.2 vs 9.2 months, P = 0.03). T-DM1 had a better safety profile compared to trastuzumab; 46% grade 3 or 4 events were reported with T-DM1 and 89% in trastuzumab arm. Based on the optimal safety profile of T-DM1, the median duration of T-DM1 was 10 months compared to 5.5 months of docetaxel and 8.1 months of trastuzumab. In the T-DM1 arm, the most frequent adverse events were fatigue (49.3%), nausea (47.8%) and increased AST (39.1%). In this study, no significant cardiotoxicity was observed with T-DM1.

The landmark phase 3 EMILIA study compared T-DM1 with the standard second-line treatment of HER2-positive advanced breast cancer. Eligibility criteria included patients who had documented progression of HER2-positive breast cancer previously treated with a taxane and trastuzumab, that is, patients who suffered from progression during or after the most recent treatment for MBC (84%) or within 6 months after treatment for early breast cancer (16%). Trastuzumab-taxane pretreated patients were randomly assigned to either 3.6 mg/kg T-DM1 or lapatinib plus capecitabine (30.8%; 95% CI: 26.3–35.7; P < 0.001). No unexpected safety signal or concern was observed from this study with thrombocytopenia (12.9%) and elevated AST/ALT (2.9%) as observed in the Phase I study, 4.3% patients reported alopecia as compared to 66.7% for trastuzumab and lapatinib. Alopecia or hair loss was either minimal or absent during TDM1 therapy. In the first line phase II study, 4.3% patients reported alopecia as compared to 66.7% for trastuzumab and docetaxel.

Thrombocytopenia
Thrombocytopenia is the most common grade 3 or higher adverse event and is the dose limiting toxicity (DLT), as seen in Phase II trials. It is reversible and starts as early as day 1, reaches nadir by day 8 and recovers by day 18. A semiphysiologic PK/PD model showed that nadir occurs after cycle 1 and eventually stabilize by cycle 8. A live imaging assay showed TDM1 uptake by megakaryocytes and platelets independent of both HER2 and Fc gamma-RIIA receptors and subsequent disruption of the microtubule cytoskeleton. On weekly administration, TDM1 caused thrombocytopenia of grade 3 or 4 in 10.7% patients. A phase II study showed 3% patients with grade 3 or higher grade thrombocytopenia in trastuzumab-docetaxel arm as compared to 8.7% in TDM1 arm. However, no grade 3 or more hemorrhagic events were noted. Hence, thrombocytopenia is transient and a well tolerated side effect of TDM1.

Transaminitis
About 42% patients had grade 1-2 elevated liver enzymes as observed in the Phase I study. Grade 3 transaminitis was observed in <10% patients when TDM1 was administered weekly. A grade 1-2 transaminitis was observed in 8.7% patients in TDM1 as compared to 0% in patients receiving trastuzumab plus docetaxel.

Cariotoxicity
Trastuzumab is known to cause systolic dysfunction. It is still not clear whether DM1 deposition to the myocardium has any long-term complications. The completed trials have demonstrated that treatment with TDM1 leads to 40% decrease in amount of trastuzumab being delivered during each cycle. A baseline of EF >50% was required for entering into the TDM1 Phase II studies and they showed no dose limiting cardiotoxicities with a minimal effect on QT prolongation. Currently a separate study is evaluating cardiac safety of TDM1 after administration of doxorubicin plus cyclophosphamide or 5-flouracil plus epirubicin and cyclophosphamide in HER2 positive early stage breast cancer.

Alopecia
Alopecia or hair loss was either minimal or absent during TDM1 therapy. In the first line phase II study, 4.3% patients reported alopecia as compared to 66.7% for trastuzumab and docetaxel.

Neuropathy
A grade 1-2 sensory neuropathy similar to vinca alkaloids was reported in 10.7% patients in the I phase I trials.

CONCLUSION
T-DM1 is the first successful anti-HER2 ADC that permits selective release of the drug within the targeted breast cancer

DRUG SAFETY PROFILE
As per phase III Emilia trial, the most common grade 3 or 4 adverse effects were thrombocytopenia (12.9%), elevated AST (4.3%) and ALT (2.9%). Other less frequent side effects include fatigue, nausea, anemia, hypokalemia, alopecia, and neuropathy.
cells. In the United States, T-DM1 is indicated specifically for treatment of HER2-positive metastatic breast cancer in patients who have been treated previously with trastuzumab and a taxane, and who have already been treated for metastatic breast cancer or developed tumor recurrence within 6 months of adjuvant therapy. The recommended dose of T-DM1 for therapy is 3.6 mg/kg q3w and is generally safely tolerated. The most common adverse effects of trastuzumab emtansine were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, transaminitis, and constipation. As evidenced by the results of the EMILIA study, it has shown clinical and statistically significant survival benefits in patients with unresectable, locally advanced or metastatic HER2-positive breast cancer after treatment with taxane-trastuzumab in comparison to lapatinib-capecitabine. As of 2013, there are several clinical trials being planned to identify other indications for T-DM1. The MARIANNE study compares taxane plus trastuzumab vs T-DM1 vs T-DM1 plus pertuzumab as a first-line treatment for patients with HER2 positive unresectable locally advanced or metastatic breast cancer.[34] The ongoing TH3RESA study is comparing T-DM1 vs the physician’s treatment choice for patients with HER2 positive metastatic breast cancer who were previously treated with trastuzumab and lapatinib.[37] There is also a phase 3 trial comparing T-DM1 to physician’s choice of taxane for the treatment of HER2 positive gastric cancer.[38] More trials are needed in the future to clarify the role of T-DM1 in the treatment armamentarium for the management of HER2-positive metastatic breast cancer patients.

REFERENCES


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37. ClinicalTrials.gov NCT01419197 A Study of Trastuzumab Emtansine in Comparison With Treatment of Physician’s Choice in Patients With HER2-Positive Breast Cancer Who Have Received at Least Two Prior Regimens of HER2-Directed Therapy (TH3RESA).

38. ClinicalTrials.gov NCT01641939 A Study of Trastuzumab Emtansine Versus Taxane in Patients With Advanced Gastric Cancer.


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